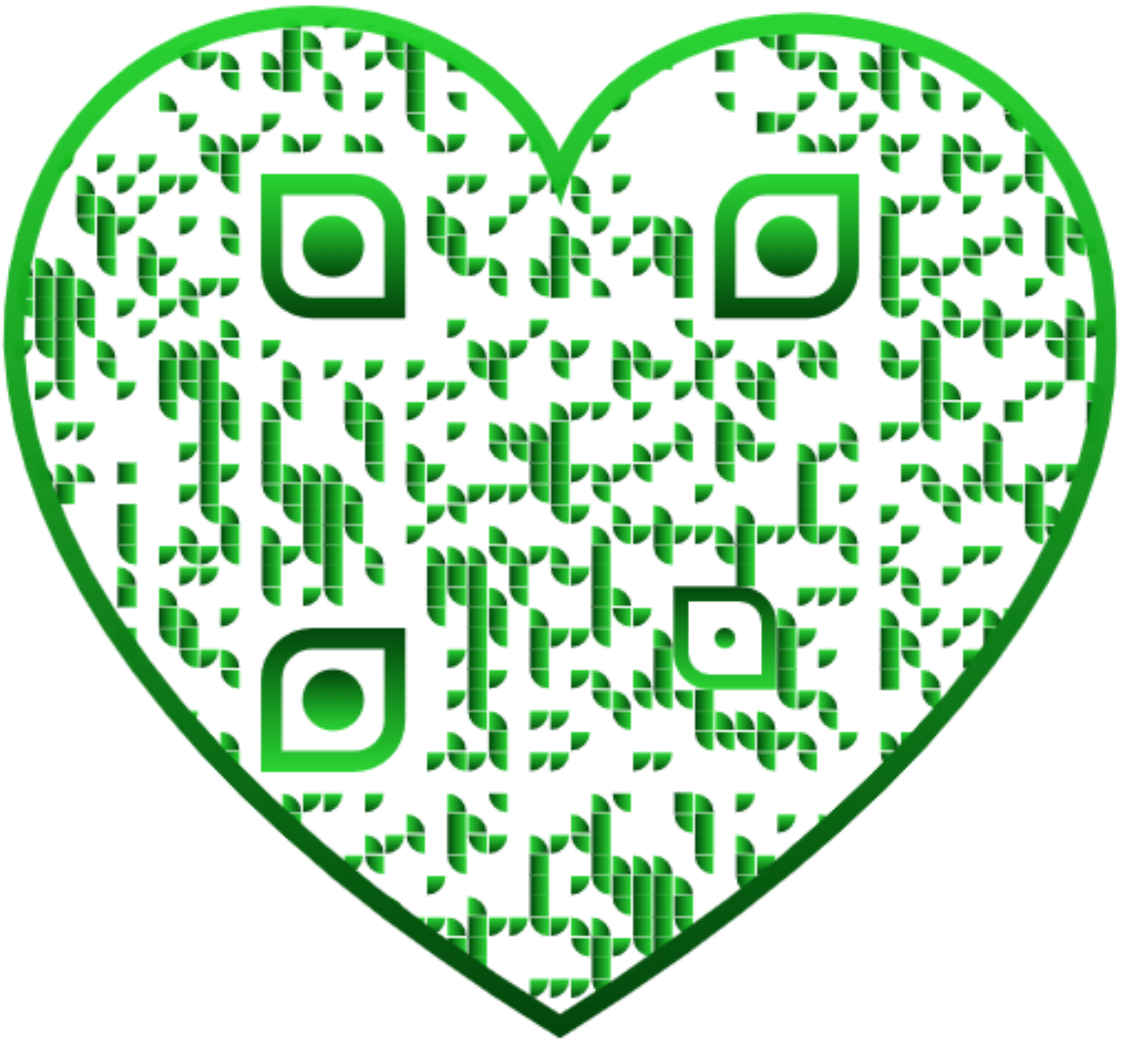
Capsules

- **Hard Gelatin Capsules**
- **Soft Gelatin Capsules**



Hard Gelatin Capsules

Introduction

- Definition
  - The word capsule is used to describe an edible package made from gelatin or other suitable material which is filled with medicines to produce a unit dosage, mainly for oral use.
  - Capsules are solid dosage forms with hard or soft shells.
  - They are of various shapes and sizes and contain a single dose of one or more active ingredients.
  - They are intended for oral administration.

- Mothes and Dublanc,
  - Inventers of the gelatin capsule
  - Patented (1834) for a method for producing single-piece, olive-shaped, gelatin capsules,
- The two - piece telescoping capsule, invented by James Murdock (1848), was patented in England in 1865.

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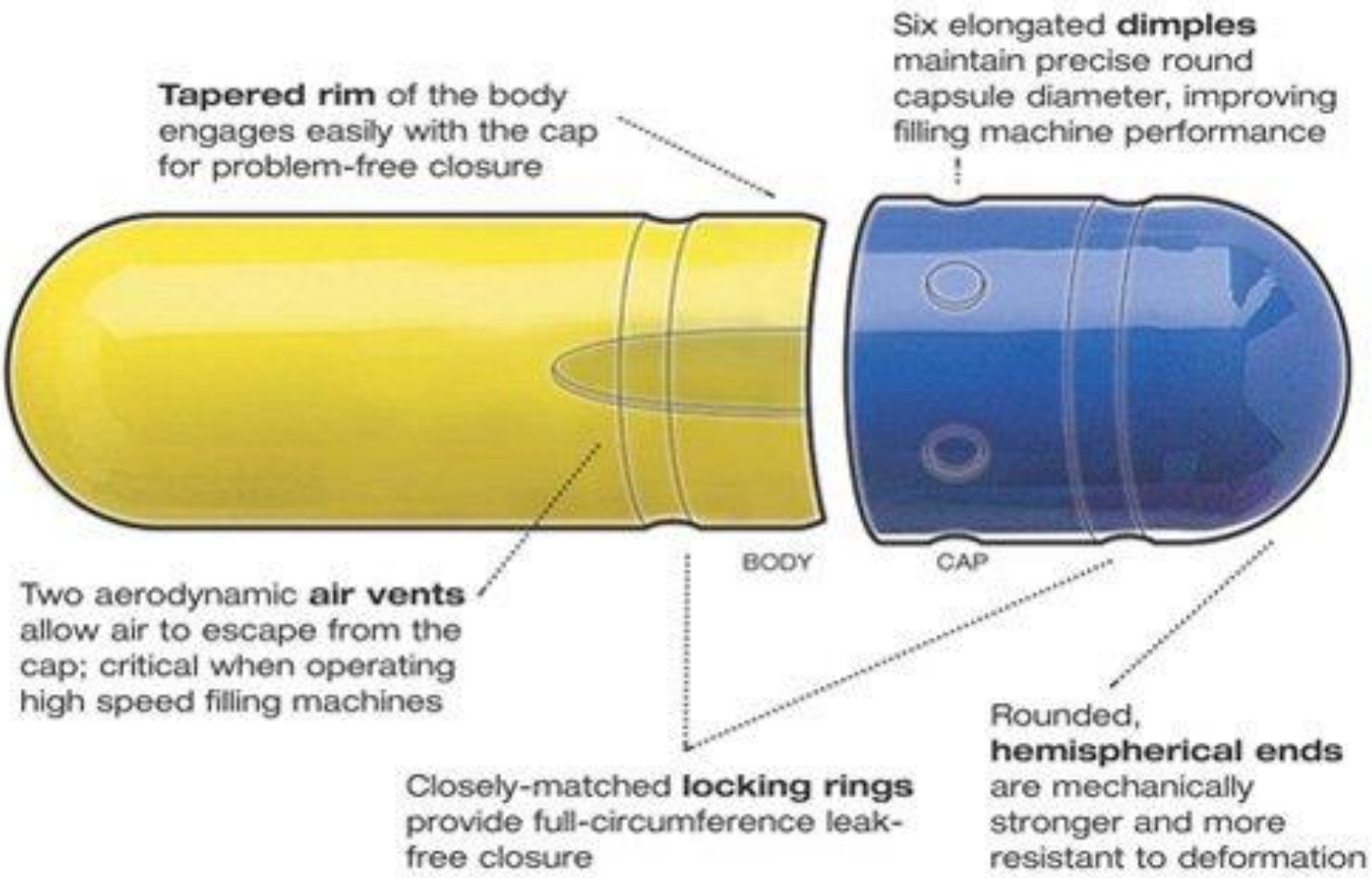
- Hard capsules have shells consisting of two prefabricated cylindrical sections that fit together.
  - One end of each section is rounded and closed and the other is open. (The hard capsule consists of two pieces (the "Cap" and "Body")
  - The contents of hard capsules are usually in solid form (powder or granules).


Six elongated **dimples** maintain precise round capsule diameter, improving filling machine performance
Tapered rim of the body engages easily with the cap for problem-free closure
BODY
CAP
Two aerodynamic **air vents** allow air to escape from the cap; critical when operating high speed filling machines
Closely-matched **locking rings** provide full-circumference leak-free closure
Rounded, **hemispherical ends** are mechanically stronger and more resistant to deformation

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- Capsules have several the advantages:
  - Elegance, ease of use and portability;
  - Provide a smooth, slippery, easily swallowed shell for drugs;
  - Mask unpleasant taste or odor;
  - Economically produced in large quantities and in a wide range of colors;
  - They generally provide ready availability of the contained drug.

- Limitations:
  - Capsules should not usually be used for the administration of extremely soluble materials (e.g. KCl, KBr, or NH_4Cl);
  - Capsules should not be used for highly efflorescent or deliquescent materials.
    - Efflorescent materials may cause the capsules to soften
    - Deliquescent powder may dry the capsule shell to excessive brittleness
      - (This may be retarded or prevented by the use of small amounts of inert oils in the powder mixture??)

Raw materials

- The raw materials used in the manufacture of both types of capsule are similar.
  - Both contain: Gelatin, water, colorants and optional materials such as process aids and preservatives.
  - In addition, soft capsules contain various **plasticizers**.

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Gelatin

- Gelatin is the major component of the capsule,
  - The reason for this is that gelatin possesses some basic properties:
    - It is non-toxic, widely used in foodstuffs, and acceptable for use worldwide,
    - It is readily soluble in biological fluids at body temperature,
    - It is a good film-forming material, producing a strong flexible film,
    - Solutions of high concentration, 40% w/v, are mobile at 50°C,

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- Gelatin is a heterogeneous product derived by irreversible hydrolytic extraction of treated animal collagen.
- Its physical and chemical properties are mainly functions of:
  - Parent collagen
  - Method of extraction
  - pH value
  - Thermal degradation, and
  - Electrolyte content

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- Animal skins and bones are the raw materials used for the manufacture of gelatin.
  - The bone gelatin produces a tough, firm film, but tends to be hazy and brittle.
  - The pork skin gelatin contributes plasticity and clarity to the blend, thereby reducing haze or cloudiness in the finished capsule.

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- There are two main types of gelatin:
  - **Type A**, which is produced by acid hydrolysis, and has isoelectric point of in around pH 9.
  - **Type B**, which is produced by basic hydrolysis and has isoelectric point of in around pH 4.7.
- Although capsules may be made from either type of gelatin, the usual practice is to use a mixture of both types as dictated by availability and cost consideration.

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- The acid process takes about 7-10 days and is used mainly for animal skins, because they require less pretreatment than do bones.

- The basic process takes about 10 times as long and is used mainly for bovine bones

  - The bones must first be decalcified by washing in acid to give a soft sponge-like material, called ossein;

  - The ossein is then soaked in lime for several weeks

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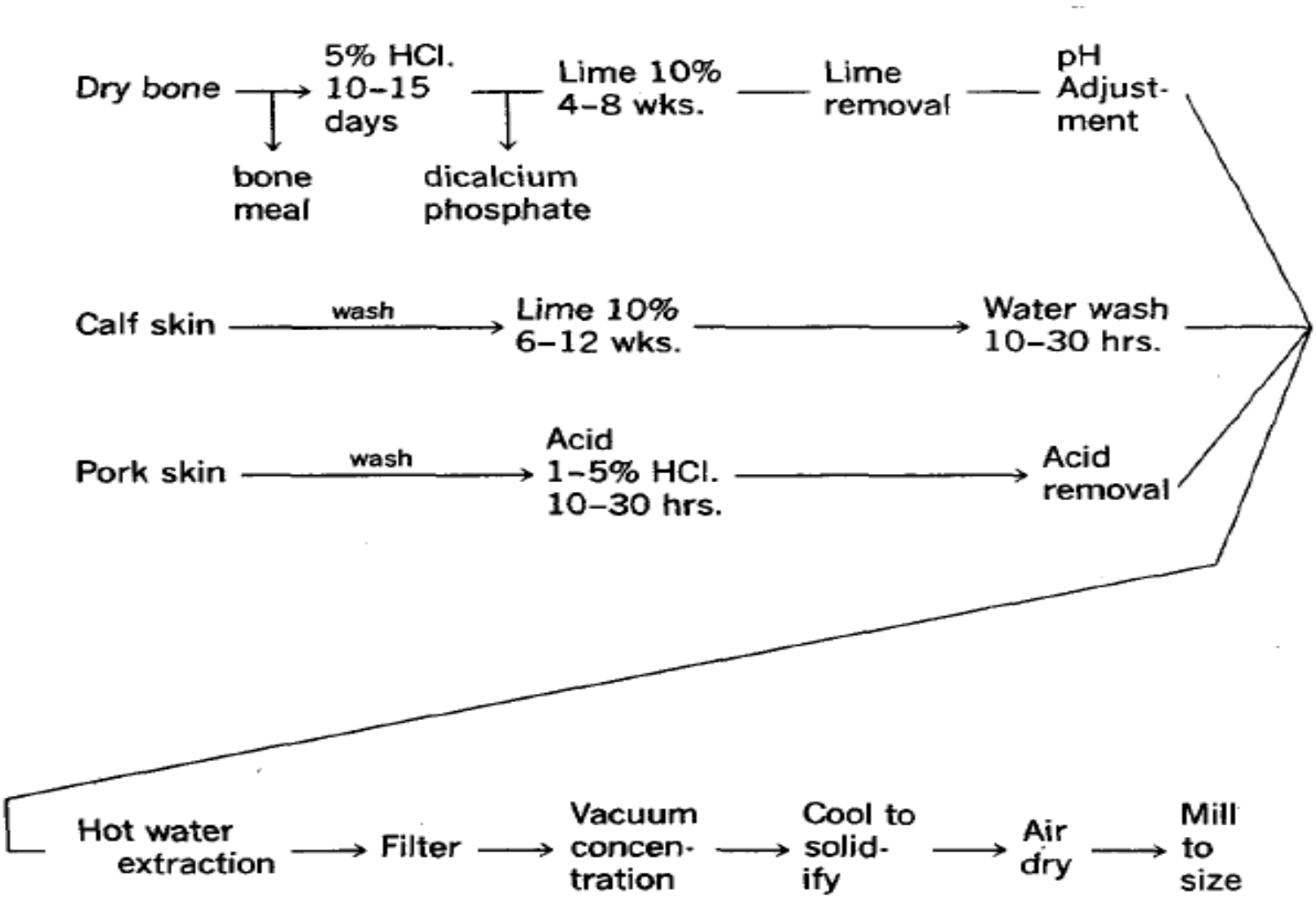
- After hydrolysis the gelatin is extracted from the treated material using hot water.
  - The first extracts contain the gelatin with the highest physical properties, and as the temperature is raised the quality falls.
- The resulting weak solution of gelatin is concentrated in a series of evaporators and then chilled to form a gel.
- This gel is then extruded to form strands, which are then dried in a fluidized-bed system
- The dried material is graded and then blended to meet the various specifications required


Dry bone
5% HCl.
10–15
days
bone
meal
dicalcium
phosphate
Lime 10%
4–8 wks.
Lime
removal
pH
Adjust-
ment
Calf skin
wash
Lime 10%
6–12 wks.
Water wash
10–30 hrs.
Pork skin
wash
Acid
1–5% HCl.
10–30 hrs.
Acid
removal
Hot water
extraction
Filter
Vacuum
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tration
Cool to
solid-
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Air
dry
Mill
to
size

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- The properties of gelatin that are most important to the capsule manufacturers are the Bloom strength and the viscosity.

- The Bloom strength is a measure of gel rigidity.

  - It is determined by preparing a standard gel (6.66% w/v) and maturing it at 10°C.

  - It is defined as the load in grams required to push a standard plunger 4 mm into the gel.

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Colorants

- The colorants that can be used are of two types: water-soluble dyes or insoluble pigments
- The dyes used are mostly synthetic in origin and can be subdivided in to
  - the azo dyes - those that have an -N=N- linkage and
  - the non-azo dyes, which come from a variety of chemical classes.

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- Most dyes used currently are of the non-azo class
  - erythrosine (E127), indigo carmine (E132) and quinoline yellow (E104)
- Two types of pigment are used
  - Iron oxides (E172), black, red and yellow, and
  - Titanium dioxide (E171), which is white and used to make the capsule opaque

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Process aids

- Sodium lauryl sulphate functions as a wetting agent
  - To ensure that the lubricated metal moulds are uniformly covered when dipped into the gelatin solution

Empty capsule manufacturing

- Steps in empty capsule manufacturing:
    1. Dipping
    2. Spinning
    3. Drying
    4. Stripping
    5. Trimming, and
    6. Joining the capsules

- Dipping
  - Large number of pairs of pins are dipped into a gelatin solution of carefully controlled viscosity to form caps and bodies simultaneously
- Spinning
  - the pins are rotated to distribute the gelatin uniformly, during which time the gelatin may be gelled by a blast of cool air

- Drying
  - The pins are moved through a series of controlled air drying kilns for the gradual and precisely controlled removal of water
- Stripping
  - The capsules are stripped from the pins by bronze jaws

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- Trimming (cutting)
  - Trimmed to length by stationary knives while the capsule halves are being spun in chucks or collets
- Joining the capsules
  - After being trimmed to exact length, the cap and body sections are joined and ejected from the machine
  - The entire cycle of the machine lasts approximately 45 min

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- Thickness of the capsule wall is controlled by:
  - viscosity of the gelatin solution,
  - speed and time of dipping,
  - mold pin dimension,
  - precise drying,

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- Empty capsules are subject to size variation as a result of moisture content variation,
  - This can be caused by exposure to extreme variations in absolute humidity or elevated temperature
- Unopened shipping containers are usually adequate protection against these changes
  - Open storage under either high or low humidity conditions should be minimized

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- Exposure to extremely high or extremely low humidity conditions for extended periods after the containers are opened causes the capsules to either gain or lose moisture
  - At high moisture levels, the capsules absorb moisture, and may soften and become tacky
  - At low moisture levels, they become brittle and suffer dimensional changes, which may cause handling problems in the filling equipment

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- Empty capsules are usually contain moisture content between 13% and 16%
  - Below 10% moisture content, they become brittle and may shrink to the point of not fitting into the filling equipment
  - Above 16% moisture content, they may cause size problems in the filling equipment and a loss of mechanical strength

- Capsules are readily soluble in water at 37°C
  - When the temperature falls below this their solubility decreases
  - At below about 30°C they are insoluble and simply absorb water, swell and distort

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Formulation

- All formulations for filling into capsules have to meet the same basic requirements
  - capable of being filled uniformly to give a stable product.
  - release their APIs in a form that is available for absorption by the patient.
  - comply with the requirements of the Pharmacopoeias and regulatory authorities, e.g. dissolution tests.

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a) Powder formulation

- The majority of products for filling into capsules are formulated as powders,
- These are typically mixtures of the active ingredient together with a combination of different types of excipients,
- The excipients selection depend upon:
  - The properties of the active drug
  - Its dose, solubility, particle size and shape
  - The size of capsule to be used

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- The easier active compounds to formulate are low-dose potent ones which in the final formulation occupy only a small percentage of the total volume (<20%),
- Formulation for filling properties:
  - There are three main factors in powder formulation:
    - Good flow, (using free-flowing diluent and glidant)
    - No adhesion (using lubricant)
    - Cohesion (plug-forming diluent)

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- The factor that contributes most to the uniform filling of capsules is good powder flow.
- Low-dose actives can be made to flow well by mixing them with free-flowing diluents, e.g. lactose.
- Packing is assisted by mechanical devices on the filling machines.
- When space is limited then either glidants, or lubricants, e.g. magnesium stearate, are added, enabling the dosing devices to function efficiently

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1) Formulation for release of active ingredients:

- The first stage in active ingredient release is disintegration of the capsule shell.
  - When capsules are placed in a suitable liquid at body temperature, the gelatin starts to dissolve and within 1 minute the shell will split,
- With a properly formulated product the contents will start to empty out before all the gelatin has dissolved

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- The rate-controlling step in capsule disintegration and product release is the formulation of the contents, which ideally should be hydrophilic and dispersible.

- The factors that can be modified to make the active ingredients readily available depend upon their properties and those of any excipients being used.

- APIs have a fixed set of physico-chemical properties which, except for the particle size, are out of the control of the formulator.

  - Particle size influences the rate of absorption for several compounds.

- Diluents are considered inert materials
  - Although they are relatively inert chemically, they do play a role in release.
  - The diluent used should be chosen in relationship to the solubility of the active drug.
    - If a soluble diluent such as lactose is added to a poorly soluble compound it will make the powder mass more hydrophilic, enabling it to break up more readily on capsule shell disintegration.
    - APIs that are readily soluble are best mixed with insoluble diluents (e.g. starch or MCC)

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- Some excipients (e.g. lubricants and glidants) are added to formulations to improve their filling properties, and these can sometimes have an effect on release.
  - The most commonly used lubricant for both encapsulation and tableting is magnesium stearate.
  - Dissolution rate will be greatly reduced at the highest level of magnesium stearate.

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- The increased dissolution can be achieved in two ways:
  - By the addition of either surfactants (e.g. sodium lauryl sulphate) or disintegrants
  - Super disintegrants are used that either
    - Swell many fold on absorbing water (e.g. sodium starch glycolate and croscarmellose) or
    - That act as wicks, attracting water into the plug, e.g. crospovidone.

2) Formulation for position of release:

- Many products are formulated to release their contents in the stomach
  - This may not always be the best place for the absorption of the API,
  - Capsule formulation can be readily manipulated to release their contents at various positions along GIT.

E.g. Floating capsules

Enteric coated capsules

Capsule filled with enteric coated pellets

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- Certain compounds are absorbed only at specific locations along the intestines.
- This has been achieved in two ways:
  - Products can be formulated to give a prolonged release and filled into a capsule that is enteric coated,
  - Products can coated with polymers that are enteric and are soluble only at higher pHs, 6-7.

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- Currently many new chemical entities are proteins or polypeptides.
- To make an oral dosage form for these drugs it is necessary to deliver them to the colon,
  - The release mechanisms for these capsules are based on specific colonic conditions.

    E.g. coatings that are disrupted by colon-specific enzymes or by pressure.

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- Not all capsules administered by the oral route are intended for GIT
  - Capsules can be used for products for **inhalation**
    - The active ingredient, which is micronized, is filled into the capsule either 'as is' or dispersed on a carrier particle.
    - The product is administered by using a special inhaler
    - A capsule is placed in the device and the powder is released either by
      - the halves of the capsule being forced apart or
      - the capsule wall being punctured by sharp pins

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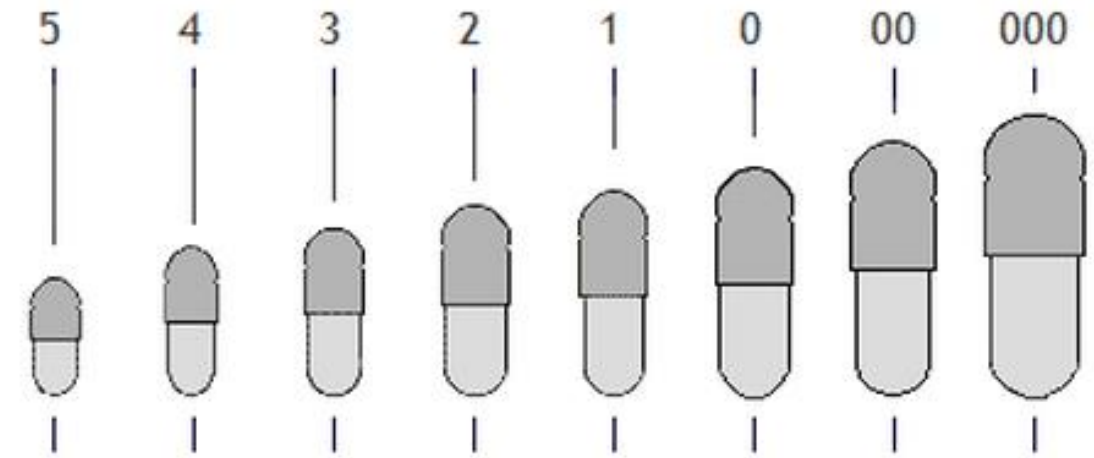
Capsule Filling

Capsules size

- Empty capsules are available in various sizes
- The ones most commonly employed for human use range from size 0, the largest, to size 5, the smallest.
- Size 00 capsules may occasionally be required because of the volume of material to be filled



mg of Aspirin	65	130	195	260	335	490	650	975
mL of liquid	0.13	0.2	0.3	0.37	0.5	0.68	0.95	1.37

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Capsule Size	Approx. Volume (ml)	Quinine Sulfate (g)	Sodium Bicarbonate (g)	Acetyl-salicylic Acid (g)	Bismuth Subnitrate (g)
0	0.75	0.33	0.68	0.55	0.8
1	0.55	0.23	0.55	0.33	0.65
2	0.4	0.2	0.4	0.25	0.55
3	0.3	0.12	0.33	0.2	0.4
4	0.25	0.1	0.25	0.15	0.25
5	0.15	0.07	0.12	0.1	0.12

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A. Filling of powder formulations

Bench-scale filling

- For filling small quantities of capsules, in community pharmacy, in hospital pharmacy, or in industry for special prescriptions or trials,

- There are several simple pieces of equipment available for doing this, e.g. Feton, Labocaps.

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- These consist of sets of plastic plates which have predrilled holes to take from 30 to 100 capsules of a specific size.
  - Empty capsules are fed into the holes,
  - The bodies are locked in their plate by means of a screw and the caps in their plate are removed,
  - Powder is placed on to the surface of the body plate and is spread with a spatula so that it is filled into the bodies,
  - The cap plate is then repositioned over the body one and the capsules are rejoined using manual pressure.

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Industrial-scale filling

- The machines for the industrial-scale filling of hard gelatin capsules come in great variety of shapes and sizes, varying from semi- to fully automatic.

- Automatic machines can be either continuous in motion or intermittent.

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- The dosing systems can be divided into two groups:
  - **Dependent**: dosing systems that use the capsule body directly to measure the powder.
  - **Independent**: dosing systems where the powder is measured independently of the body in a special measuring device.

- Dependent dosing systems

  - Empty capsules are fed into a pair of ring holders, the caps being retained in one half and the bodies in the other.

  - The body holder is placed on a variable-speed revolving turntable; the powder hopper is pulled over the top of this plate, which revolves underneath it.

  - In the hopper a revolving auger forces powder down into the capsule bodies

- Independent dosing systems
  - Are fully automatic and use dosing mechanisms that form a 'plug` of powder
  - There are two types of plug-forming machine:
    - Those that use a **'dosator`** system and
    - Those that use a 'tamping **finger** and dosing **disc**' system

- Dosators
  - Consists of a dosing **tube** inside which there is a movable spring-loaded piston, thus forming a variable-volume chamber in the bottom of the cylinder
  - Tube is lowered open end first into powder bed, that enters the tube to fill the chamber and form a plug.
  - Raised from powder bed and positioned over capsule body
  - Piston is lowered, ejecting the powder plug into the capsule body

- The weight of powder filled can be adjusted
  - By altering the position of the piston inside the tube, i.e. increasing or decreasing the volume, and
  - By changing the depth of the powder bed

- Tamping finger and dosing disc
  - The dosing disc forms the bottom of a revolving powder hopper.
  - This disc has in it a series of sets of accurately drilled holes in which powder plugs are formed by several sets of tamping fingers
  - At each position the fingers push material into the holes, building up a plug before they index on to the next position.
  - At the last position the finger pushes the plug through the disc into a capsule body.

- The powder fill weight can be varied
  - by the amount of insertion of the fingers into the disc,
  - by changing the thickness of the dosing disc, and
  - by adjusting the amount of powder in the hopper

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B. Pellet filling

- They are filled on an industrial scale using machines adapted from powder use.
  - All have a dosing system based on a chamber with a volume that can easily be changed.
  - Pellets are not compressed in the process and may have to be held inside the measuring devices by mechanical means, e.g. either by inverting the dosator or by applying a suction to the dosing tube.

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C. Tablet filling

- Tablets are placed in hoppers and allowed to fall down tubes, at the bottom of which is a gate device that will allow a set number of tablets to pass.

- Most machines have a mechanical probe that is inserted into the capsule to check that the correct number of tablets is transferred

- Tablets are normally film coated to prevent dust, and are sized so that they can fall freely into the capsule body

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D. Semisolid and liquid filling

- Liquids can easily be dosed into capsules using volumetric pumps
- The problem after filling is to stop leakage from the closed capsule
  - This can be done in one of two ways, either by formulation or by sealing of the capsule

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- Formulations that are semisolid at ambient temperatures and can be liquefied for filling:
  - By either heating thermosoftening mixtures, or
  - By stirring thixotropic mixtures
- After filling they cool and solidify, or revert to their resting state in the capsule to form a semisolid plug

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Capsule sealing

Gelatin banded sealing

- Some manufacturers make tamper evident capsules by sealing the joint between the two capsule parts using gelatin solution
  - Once manufacturer makes distinctive looking capsules by sealing them with a colored band of gelatin
  - If removed, the band cannot be restored without expert resealing with gelatin

Heat welding

- Capsules may also be sealed through a heat welding process that fuses the capsule cap to the body through the double wall thickness at their juncture
  - The process results in a distinctive ring around the capsule where heat welded.

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Thermally bonding

- This process uses a liquid wetting agent that lowers the melting point in the contact area of the capsule's cap and body, and then thermally bonds the two parts using low temperature (40 – 45 ^{O}C).

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Finishing

- Finished capsules from all filling equipment require some sort of dusting and/or polishing,
- Dusting or polishing operations vary according to:
  - The type of filling equipment used,
  - The type of powder used for filling, and
  - The individual desires for the finished appearance of the completed capsules

- Polishing methods most commonly used are

1. Pan polishing

- Because of its unique design (primarily in the area of airflow), the Accela Cota tablet coating pan may used to dust and polish capsule.

- A polyurethane cloth liner placed in the pan and the liner is used to trap the removed dust as well as to impart a gloss to the capsules

2. Cloth dusting

- In this method, the bulk- filled capsules are rubbed with a cloth that may or may not be impregnated with an inert oil
- This procedure is a hand operation, but one that can handle reasonable volumes, and that results in a positive method for removal of resistant material
- It impart gloss to capsules

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3. Brushing

- Capsules are fed under rotating soft brushes, which serve to remove dust from the capsule shell
- This operation must be accompanied by a vacuuming for dust removal
- Some materials are extremely difficult to remove by brushing, even to the point of impregnating the brushes and causing scratches or deformation of the capsules

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Quality control of filled HGC

- Read …

Soft Gelatin Capsule

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- Soft gelatin capsules are capsules in which the mechanical properties of gelatin have been manipulated by the addition of a **plasticizer** resulting in a more **flexible** capsule

- Soft gelatin capsules are used to encapsulate and hermetically seal liquids, suspensions, pasty materials, dry powders, and even preformed tablets

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- Owing to their special properties and advantages, soft gelatin capsules are used in a wide variety of industries.
- Their pharmaceutical applications are:
  - As an oral dosage form of proprietary products,
  - As a suppository dosage form for rectal or vaginal use,
  - As a specialty package in tube form for single dose application of topical, ophthalmic, and otic preparations,
  - In the cosmetic industry, for breath freshener, perfumes, bath oils and various skin creams

- Standard Shapes and Size

Ovals
minims: 1.5-30.0
cc: 0.092-1.848

Oblongs
minims: 2.3-22.0
cc: 0.142-1.355

Rounds
minims: 0.75-41.0
cc: 0.046-2.526

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The nature of the Capsule Shell

- The capsule shell is basically composed of gelatin, a **plasticizer**, and water.
- It may contain additional ingredients
  - Preservatives, coloring and opacifying agents, flavorings, sugars, acids to achieve desired effects

Gelatin

- The gelatin is USP grade with additional specifications required by the capsule manufacturer
- The additional specifications concern the Bloom strength, viscosity, and iron content of the gelatins used
  - The Bloom or gel strength of gelatin is a measure of the cohesive strength of the cross-linking that occurs between gelatin molecules and is proportional too the molecular wt of the gelatin

- Bloom or gel strength is determined by measuring the weight in grams required to move a plastic plunger that is 0.5 inches in diameter 4 mm into a 6.66 % W/V gelatin gel that has been held at 10°C for 17 hours
  - ranges from 150 to 250 g
  - with all other factors being equal, the higher the Bloom strength of the gelatin used, the more physically stable is the resulting capsule shell

- The cost of gelatin is directly proportional to its film strength (bloom strength)
  - the higher bloom strength are only used
    - when necessary to improve the physical stability of a product or
    - for large capsules (over 50 minims), which require greater structural strength during manufacture

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- Viscosity of gelatin, determined on a 6.66 % W/V concentration of gelatin in water at 60°C, is a measure of the molecular chain length and determines the manufacturing characteristics of the gelatin film
  - The viscosity for gelatin can range from 25-45 millipoise to make use of a standard formulation and thus conform to standard production conditions

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- The desired film characteristics are usually based on standard gelatin formulations
  - which allow production at a set sealing temperature and definite drying conditions, and produce a firm, nontacky, nonbrittle film and pharmaceutically elegant product.
- Low viscosity high Bloom (180-250g) gelatin are used in conjugation with the capsulation of hygroscopic vehicle and solid.

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- Iron always present in the raw gelatin, and its concentration usually depends on the Iron content of the large quantities of water used in its manufacture.

- Gelatins used in the manufacture of **SGCs** should not contain more than 15 ppm of iron

  - Because of its effect on dyes and

  - Its possible color reactions with organic compounds

Plasticizer

- The plasticizers used with gelatin in soft capsule manufacture include:
  - **Glycerin** USP, **Sorbitol** USP, Pharmaceutical Grade Sorbitol Special, and combinations of these are the most prevalent.
- The ratio by weight of dry plasticizer to dry gelatin determines the "hardness" of the gelatin shell, assuming that there is no effect from the capsulated material.

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- In general, the additional components of the gelatin mass are limited in their use by:
  - the amounts required to produce the desired effect
  - their effect on capsule manufacture
  - economic factors

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Colorants

- Color of the SGC can be definitely affected by the color or type of material capsulated
- As a general rule, the color of the capsule shell should never be lighter in hue than the capsulated material
- More specifically, darker colors are more appropriate for large-size (14 to 20 minim oblong) oral products, since they will not accentuate the size.

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- As a rule, clear color is employed with clear type fill materials, and opaque colors are used with suspension.

- For special effects or identification purposes, two colors, both opaque or one opaque and one clear, may be chosen since the manufacturing process involves two gelatin films.

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The Nature of the Capsule Content

- The formulation of the capsule content for each product is individually developed to fulfill the specifications and end-use requirements of the product.

- The content of a soft gelatin capsule is a liquid, or a combination of miscible liquids, a solution of a solid(s) in liquid(s), suspension of solid(s) in liquid(s) or dry powder.

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Liquids

- Are an essential part of the capsule content.
- Those liquids that are both water- miscible and volatile **cannot** be included as major constituents of the capsule content since they can migrate to the hydrophilic gelatin shell and volatilize from its surface.
- Similarly, gelatin plasticizers such as glycerin and propylene glycol **cannot** be major constituents of the capsule content.

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- As minor constituents (about 5% of the capsule content) water and alcohol can be used as co-solvents to aid in the preparation of solutions for capsulation.

- Up to 10% glycerin and/or propyline glycol can be used as co-solvents with poly ethylene glycol or other liquids that have a shell-hardening effect when capsulated alone.

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- All liquids, solutions, and suspensions for capsulation should be homogeneous and air-free and preferably should flow by gravity at room temperature.

- In general, liquids ranging in viscosity from ethyl ether (0.222 cp at 25°C) to heavy adhesive mixtures (exceeding 3000 cp at 25°C) may be encapsulated,

  - But, there are some exceptions since the property of viscosity alone is not the sole criteria.

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- Liquids that exhibit the rheological property of tack or tackiness, such as glycerin (954 cp at 25°C), are exceptions, since such liquids can eventually cause the binding of slide valves and pumps in the capsule filling machine

- Preparations for encapsulation should have a pH between 2.5 and 7.5.

  - Since, preparations that are more acidic can cause hydrolysis and leakage of the gelatin shell.

  - Preparations that are more alkaline can tan the gelatin and thus affect the solubility of the shell.

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- The capsulation of water-immiscible liquids is the simplest form of soft gelatin capsulation and usually requires little or no formulation.
  - The minimum size capsule depends on the dosage desired, the minimum fill volume being calculated from the specific gravity of the liquid

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Solids

- Solids that are not sufficiently soluble in liquid or in combinations of liquids are encapsulated as suspensions.

- Most organic and inorganic solid or compounds may be capsulated.

  - Such materials should be 80 mesh or finer in particle size, owing to certain close tolerances of the encapsulation equipment and for maximum homogeneity of the suspension

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- Many compounds can not be capsulated, owing to their solubility in water and thus their ability to affect the gelatin shell,

- Also, any substance that is unstable in the presence of moisture (e.g., aspirin) would not exhibit satisfactory chemical stability in soft gelatin capsules.

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- The capsulation of suspensions is the basis for the existence of a large group of products.
- The formulation of suspensions for capsulation follows the basic concepts of suspension technology.
  - Formulation techniques, however, can vary depending on:
    - the drug substance,
    - the desired flow characteristics,
    - the physical or ingredient stability problems
    - the biopharmarceutical properties desired

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- In most instances these techniques must be developed through the ingenuity of the formulating pharmacist however, in the formulation of suspensions for soft gelatin encapsulation, certain basic information must be developed to determine minimum capsule size

- One tool is the basic adsorption of solid to be suspended

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- the base adsorption is obtained by means of the following formula:

$$\frac{\text{Weight of Base}}{\text{Weight of Solid}} = \text{Base Adsorption}$$

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- The base adsorption mixture is milled or homogenized, and deaerated (a desiccator under vacuum is suitable), and the specific gravity taken. The specific gravity is the weight of mixture (W) per cubic centimeter or per 16.23 minims (V).

  - As in the case of liquids and solutions, the specific gravity may be used to determine the die size required for a given quantity the particular mixture.

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- The base adsorption is used to determine "minim Per gram" factor (M/g) of the solid(s).

- the minim per gram factor is the volume in minims that is occupied by one gram (S) of the solid plus the weight of liquid base (BA) required to make a capsulable mixture.

- The minim per gram factor is calculated by dividing the weight of base $\frac{(BA + S) \times V}{W} = M/g$ of solid (BA + S) by the weight of mixt ubic centimeter or 16.2.3 minims (V). A convenient formula is:

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- Thus, the lower the base adsorption of the solids and the higher the density of the mixture, the smaller the capsule will be.

- This also indicates the importance of establishing specifications for the control of those physical properties of a solid that can affect its base adsorption.

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Manufacture of soft gelatin capsule

- Soft gelatin capsules may be prepared by:
  - The **Plate process**, using a set of molds to form the capsules, or
  - **Rotary** or reciprocating die processes in which they are produced, filled, and sealed in a continuous operation

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Plate process

- A warm sheet of plain or colored gelatin is placed on the bottom plate of the mold and the medication-containing liquid is evenly poured on it,
- Then a second sheet of gelatin is carefully placed on top of the medication and the top plate of the mold is put into place,
- Pressure is then applied to the mold to form, fill, and seal the capsules simultaneously,
- The capsules are removed and washed with a solvent,

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Rotary die process

- Involves the continuous formation of a heat seal between two ribbons of gelatin, simultaneous with dosing of the fill liquid into each capsule,

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- Before the encapsulation process takes place, there are two subprocesses that are often carried out simultaneously, yielding the two components of a softgel.
  - the gel mass which will provide the soft gel shell, and
  - the fill matrix for the contents

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- The gel mass is prepared by dissolving the gelatin in water at approximately 80°C and under vacuum, followed by the addition of the plasticizer
- Once the gelatin is fully dissolved then other components, such as colours, opacifier, flavours and preservatives, may be added.
- The hot gel mass is then supplied to the encapsulation machine through heated transfer pipes by a casting method that forms two separate gelatin ribbons, each approximately 150 mm wide.

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- During the casting process the gelatin passes through the sol-gel transition and the thickness of each gel ribbon is controlled to ± 0.1 mm, in the range of about 0.5-1.5 mm.
  - The thickness is checked regularly during the manufacturing process.

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- The two gel ribbons are then carried through rollers (at which a small quantity of vegetable oil lubricant is applied) and onwards to the rotary die encapsulation tooling

- Each ribbon provides one half of the softgel

  - It is possible to make bicoloured softgels using gel ribbons of two different colours

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- The liquid fill matrix containing the active drug substance is manufactured separately
- Manufacture of the active fill matrix involves dispersing or dissolving the drug substance in the non-aqueous liquid vehicle using conventional mixer-homogenizers.

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- A number of different parameters are controlled during the preparation of the active fill matrix, depending on the properties of the drug substance
  - E.g. oxygen-sensitive drugs are protected by mixing under vacuum and/or inert gas; or an antioxidant component may be added to the formulation
  - if the drug substance is present as a suspension in the liquid fill matrix particle size of the drug should not exceed approximately 200 µm

- Rotary die encapsulation process involves careful control of three parameters:
  - Temperature
  - Timing
  - Pressure

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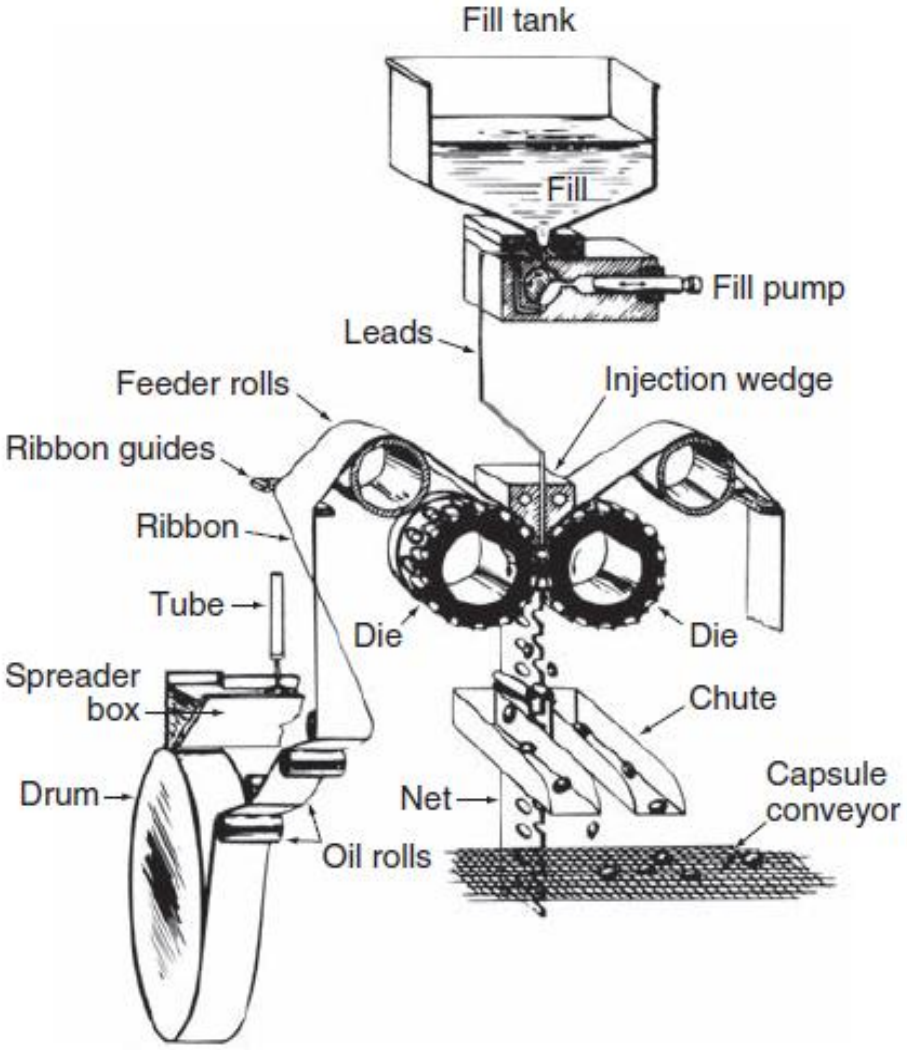
- Accurately metered volumes of the liquid fill matrix are injected from the wedge device into the space between the gelatin ribbons as they pass between the die rolls

- The wedge-shaped injection system is itself heated to approximately 40°C.


Fill tank
Fill
Fill pump
Leads
Feeder rolls
Injection wedge
Ribbon guides
Ribbon
Tube
Die
Die
Spreader box
Chute
Drum
Net
Capsule conveyor
Oil rolls

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- The injection of liquid between the ribbons forces the gel to expand into the pockets of the dies, which govern the size and shape of the softgels
- The ribbon continues to flow past the heated wedge injection system and is then pressed between the die rolls.
- Here the two softgel capsule halves are sealed together by the application of heat and pressure.
- The capsules are cut automatically from the gel ribbon by raised rims around each die on the rollers

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- After manufacture the capsules are passed through a tumble drier and then, to complete the drying process, spread on to trays and stacked in a tunnel drier that supplies air at 20% relative humidity

- Finally, the softgels are inspected and packed into bulk containers in order to prevent further drying and for storage.

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Product Quality Considerations

Ingredient specifications

- All of the ingredients of a softgel are controlled and tested to ensure compliance with pharmacopoeial specifications.

- However, additional specification tests may be added for certain excipients in order to ensure the manufacture of a high-quality softgel product.

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- The ingredient requiring the most careful control is gelatin itself

- Once a particular grade of gelatin is used in a softgel formulation the quality is controlled using parameters such as the viscosity of a hot solution and the bloom strength of the gel (bloom strength is a measure of the hardness of a gel).

In-process testing

- During the encapsulation process the four most important tests are:
  - The gel ribbon thickness
  - Softgel seal thickness at the time of encapsulation
  - Fill matrix weight and capsule shell weight
  - Softgel shell moisture level and softgel hardness at the end of the drying stage.

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- Appropriate control levels for these parameters are established during process development for each softgel product, and are applied in routine production scale manufacture.

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Finished product testing

- Finished softgels are subjected to a number of tests in accordance with compendial requirements for unit dose capsule products.

- These normally include
  - capsule appearance
  - active ingredient assay
  - fill weight and content uniformity
  - microbiological testing